Summary of Safety and effectiveness

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Dual Chamber Implantable Cardioverter Defibrillator System & Programmer Software
Device Trade Name:	Tachos DR – Atrial Tx ICD, Model 122499 Software Cartridge SWM / I-KDR.0.C, Model 339684
Applicant's Name and Address:	BIOTRONIK, Inc. 6024 Jean Road Lake Oswego, OR 97035
Date of Panel Recommendation:	None
Premarket Approval (PMA) Number:	P000009/S4
Date of Notice of Approval to Applicant:	September 9, 2002

The Tachos DR Implantable Cardioverter Defibrillator was approved on March 5, 2002, under P000009/S1 to provide ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias. The applicant submitted the current supplement to modify the device to include atrial therapies and thereby expand he indication statement. The clinical data to support the expanded indication are provided in this summary. The pre-clinical test results were in included in both the original PMA application and the PMA supplement. For more information on the data that supported the previously approved indication, the summary of safety and effectiveness data (SSED) can be obtained from the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, Maryland 20857. The summary can also be found on the FDA CDRH Internet Home page located at http://www.fda.gov/cdrh/pmapage.html.

II. INDICATIONS FOR USE

The Tachos DR – Atrial Tx Implantable Cardioverter Defibrillator (ICD) is intended to provide ventricular antitachycardia pacing and ventricular defibrillation, for automated treatment of life-threatening ventricular arrhythmias.

The device is indicated for use in ICD patients with either atrial tachyarrhythmias or who are at risk of developing atrial tachyarrhythmias.

III. CONTRAINDICATIONS

The Tachos DR – Atrial Tx is contraindicated for use in patients that have the following conditions:

- Patients whose ventricular tachyarrhythmias may have transient or reversible causes such as:
  - acute myocardial infarction
  - digitalis intoxication
  - drowning
  - electrocution
  - electrolyte imbalance
  - hypoxia
  - sepsis
- Patients with incessant VT or VF
- Patients who have a unipolar pacemaker
- Patients whose only disorder is bradyarrhythmias or atrial arrhythmias

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the labeling.

V. DEVICE DESCRIPTION

The Tachos DR – Atrial Tx ICD System is a dual-chamber rate adaptive pulse generator capable of delivering antitachycardia pacing (ATP), cardioversion, and defibrillation shock therapy for treatment of atrial and ventricular tachyarrhythmias. The device shock output ranges from 0.5 to 30 joules in the form of a biphasic waveform.

The atrial therapy features are capable of detecting and converting atrial tachyarrhythmias including atrial fibrillation (AF) and other atrial tachycardias (AT). The types of atrial tachyarrhythmia therapy available in the device include atrial ATP therapy for AT, atrial high frequency (HF) burst therapy for AF/AT, and shock therapy for AF/AT. The device allows programming of up to three (3) atrial tachyarrhythmia zones including two (2) AT zones and one (1) AF zone.

The BIOTRONIK Tachos DR – Atrial Tx Implantable Cardioverter Defibrillator System consists of implantable components (pulse generator and lead system), external programming system and various accessories used during implantation and follow-up electrophysiological (EP) procedures. The atrial and ventricular sensing and pacing leads provide enhanced detection of atrial and ventricular tachyarrhythmias.

All hardware components of the Tachos DR – Atrial Tx ICD system are identical to those in the market released Tachos DR (P000009/S1) without atrial therapies. Only the features regarding detection and treatment of atrial tachyarrhythmias are new and are implemented in the associated programmer software. The Tachos DR – Atrial Tx ICD System consists of the following:

- **Tachos DR – Atrial Tx Implantable Cardioverter Defibrillator (ICD)**
  The ICD has a volume of 48 cc and weighs 84 grams. The Tachos DR –Atrial Tx has two (2) DF-1 defibrillation/cardioversion and two (2) IS-1 pacing/sensing header ports.

- **Commercially Available BIOTRONIK ICD leads (P980023)**
  ICD leads that contain two (2) high energy shock coils.

- **Commercially Available IS-1 Atrial Sensing and Pacing lead from BIOTRONIK or other manufacturers**

- **BIOTRONIK Programmer**
  BIOTRONIK's TMS 1000^{PLUS} and EPR 1000^{PLUS} are commercially available programming systems that are utilized to interrogate and program BIOTRONIK's ICDs and pacemakers. These programmers use write-protected (read-only) PCMCIA Flash-EPROM cartridges.

- **SWM 1000 I-KDR.0.C. Programmer Software**
  PCMCIA Flash-EPROM cartridge that contains separate programmer software applications including: TMS 1000, Phylax AV, and Tachos DR – Atrial Tx.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative therapies for the treatment of life-threatening ventricular arrhythmias as deemed appropriate by the physician are based upon electrophysiology (EP) testing and other diagnostic evaluations. These include the use of antiarrhythmic medication, electrical ablation, cardiac surgery, pacemakers, and other commercially available implantable cardioverter defibrillators (ICDs).

VII. MARKETING HISTORY

The Tachos DR – Atrial Tx ICD System began distribution outside the United States in the summer of 2000. BIOTRONIK's Tachos DR ICD has not been withdrawn from any market for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Reported Adverse Events

The multi-center, non-randomized clinical investigation was designed to demonstrate the effectiveness of the Tachos DR - Atrial Tx to detect and convert atrial tachyarrhythmias in patients that require standard ICD therapy and that have a history or significant risk of atrial tachyarrhythmias.

Table 1 provides a summary of the adverse events that were reported during the clinical study regardless of whether the event was related to the ICD system. A complication was defined as a clinical event that resulted in additional invasive intervention, injury, or death. An observation was defined as a clinical event that did not result in additional invasive intervention, injury, or death.

Table 1: Reported Adverse Events

Category	Number of Patients	Percentage of Patients	Number of AEs	AEs per patient-year
Overall Complications – Totals	**23**	**17.2%**	**23**	**0.31**
Lead-Related	13*	9.7%	13*	0.17
Atrial Lead Repositioning	10	7.5%	10	0.13
Ventricular Lead Repositioning	4	3.0%	4	0.05
Non-Lead Related	**10**	**7.5%**	**10**	**0.13**
Medical	5	3.7%	5	0.07
Device-Related	3	2.2%	3	0.04
Elevated DFT's	2	1.5%	2	0.03
Overall Observations – Total	**74**	**55.2%**	**135**	**1.81**
Atrial induction shock induced VT/VF	9	6.7%	10	0.13
Detection	9	6.7%	9	0.12
Elevated DFT's	3	2.2%	3	0.04
Far-field oversensing	12	9.0%	12	0.16
Inappropriate episode termination	12	9.0%	14	0.19
Ineffective atrial therapy	4	3.0%	4	0.05
Manual atrial shock not synchronous with ventricular event	3	2.2%	3	0.04
Medical	27	20.1%	30	0.40
Patient in AT/AF	8	6.0%	8	0.11
Phantom shock	4	3.0%	4	0.05
Programmer software I-HAT.0.U/3	5	3.7%	5	0.07
Programmer software I-HAT.0.U/4	3	2.2%	3	0.04
Sensing and pacing	19	14.2%	20	0.27
T-wave oversensing	8	6.0%	8	0.11
Other	2	1.5%	2	0.03

Number of Patients = 134, Number of Patient-Years = 74.7

* One patient underwent both an atrial and ventricular lead repositioning in the same procedure.

Survival

There were 9 patient deaths reported. None of these deaths were related to the implanted ICD system. A summary of the deaths grouped into predefined categories is provided in Table 2.

Table 2: Patient Deaths - Summary

Category	Number of Patients	Percentage of Patients (n=134)
Sudden Cardiac	1	0.7%
Non-Sudden Cardiac	6	4.5%
Non-Cardiac	2	1.5%
Unexplained	0	0.0%
All Causes	**9**	**6.7%**

Potential Adverse Events

Adverse events (in alphabetical order) associated with ICD systems include the following:

- Acceleration of arrhythmias
- Air embolism
- Bleeding
- Chronic nerve damage
- Erosion
- Excessive fibrotic tissue growth
- Extrusion
- Fluid accumulation
- Formation of hematomas or cysts
- Inappropriate shocks
- Infection
- Keloid formation
- Lead abrasion and discontinuity
- Lead migration/dislodgment
- Myocardial damage
- Pneumothorax

- Shunting current or insulating myocardium during defibrillation with internal or external paddles
- Potential mortality due to inability to defibrillate or pace
- Thromboemboli
- Venous occlusion
- Venous or cardiac perforation

Additionally, the potential risks related to the atrial therapy feature of this ICD system may include the following:

- Induction of ventricular arrhythmias
- Acceleration of atrial arrhythmias
- Inappropriate atrial shocks
- Potential morbidity related to ineffective atrial shocks

Patients susceptible to frequent shocks despite antiarrhythmic medical management may develop psychological intolerance to an ICD system that may include the following:

- Dependency
- Depression
- Fear of premature battery depletion
- Fear of shocking while conscious
- Fear that shocking capability may be lost
- Imagined shocking (phantom shock)

IX. SUMMARY OF PRECLINICAL STUDIES

The following tables summarize the validation testing (safety and performance) conducted on components and subassemblies of the BIOTRONIK Tachos DR - Atrial Tx ICD System, including testing of finished devices, packaging, and shipping tests. Validation testing was performed to appropriate European, International, and National standards, in addition to internal BIOTRONIK specifications. In addition, biocompatibility testing was conducted. In Tables 4, 5, and 6, "Pass" denotes that the test results satisfied the company's device specifications.

Component Testing

Bench testing of all components of BIOTRONIK's Tachos DR – Atrial Tx ICD was successfully completed. The validation included testing of all components that are used to assemble the Tachos DR - Atrial Tx. The validation reports for all of the hardware

components are identical to what is used in the original Tachos DR PMA Supplement (P000009/S1) and are referenced in Table 3.

Table 3: Summary of Component Tests

Component	Description	Qualified With
LiS 12100	Lithium-Iodine Cell with a Nominal Voltage of 2.8 volts	Tachos DR P000009/S1
LiS 3482	Lithium Manganese Dioxide Cell with a Nominal Voltage of 6.3 volts	Tachos DR P000009/S1
High Energy Capacitors	Two 185 µF Capacitors	Tachos DR P000009/S1
Electronic Module	Hybrid Electronic Circuitry	Tachos DR P000009/S1
Header	Epoxy Header Containing two IS-1 and two DF-1 ports	Tachos DR P000009/S1
Housing	Titanium Can that Contains all of the Electronic Components and Circuitry	Tachos DR P000009/S1
Feedthroughs	One quadrapolar (IS-1) and two unipolar feedthroughs (FD-1)	Phylax AV ICD P000009

Embedded Software Testing

The embedded software contains the necessary instructions to implement the Smart Detection algorithm and other device features and functions. The embedded software is identical between the market released Tachos DR and the Tachos DR - Atrial Tx ICD and has successfully passed all validation testing as defined by BIOTRONIX's internal validation system.

The Tachos DR – Atrial Tx was evaluated according to a BIOTRONIK's internal Validation Plan (VPL) to demonstrate conformance to the design requirements, specifications and safety standards (VPL-111-539). A Validation Notification was developed (VAN-111-02-006) which references the steps of developed validation plans (VPLs) deemed applicable and required to sufficiently validate the Tachos DR – Atrial Tx. Numerous National and International standards (prEN 45502-2-2: 1998, AAMI PC 69) and internal BIOTRONIK standards have been used to validate the product's functionality and performance.

Several of the validation tests for the Tachos DR – Atrial Tx reference test results that have been repeated from previous versions of embedded software (regression testing) for the legally marketed Tachos DR regarding identical features (i.e., ventricular therapies). The embedded software testing summarized in Table 4 is limited to qualifying atrial therapies.

Table 4: Summary of Embedded Software Testing

Test Condition/Specification	Sample	Test Results (Pass/Fail)
- Noise Detection - Therapy Acceleration, Redetection, and Termination - AT/AF Detection - Dual Chamber Tacharrhythmia Transition - Atrial and Ventricular ATP Therapy - HF Therapy - Ventricular Support During Atrial ATO Therapy - Committed/Non-Committed Shock Therapy for VT/VF and AT/AF Shocks - Atrial Shock Modes (Atrial Therapy features of embedded software were tested per Internal BIOTRONIK Engineering Specifications 9727321, 8990059, and 8990065)	Current embedded software	Met Acceptance Criteria

Finished Device Testing

Testing of the fully assembled Tachos DR - Atrial Tx ICD was successfully completed. Testing of the completed device was performed with the devices after various stages of post-assembly product processing. Tests were performed with sterilized product, product prior to sterilization, and to devices that were packaged and ready for shipment. The testing is summarized in Table 5.

Table 5: Finished Device Testing

Test Condition/Specification	Quantity	Results
Verification Examination against Specification		
Conformance with Requirement Specification and Design Specification (per BIOTRONIK's Internal Specifications)	1	Met Acceptance Criteria
Environmental Test		
- Visual Inspection of General Packaging Design and Accompanying Documentation - Drop Test - Transportation Test - Humidity Storage - Wipe Test - Small Blister and Outer Label - Sterilization Process - Protection of the Patient from Injury caused by Heat - Ultrasonic Resistance - Vibration Test - Mechanical Shock Test - Protection from Damage caused by Air Pressure Changes - Protection from Damage caused by Temperature Changes (per EN 45502-1:1998, prEN 45502-2-2:1998, and BIOTRONIK's Internal Validation Standards)	1-5	Met Acceptance Criteria
Header Tests		
- In-Vitro headerpost test 500 hours - Dimensional and Visual Inspection f the Header - verification of the Compliance and Effectiveness of Informative Risk Reduction Measures from Product Risk Analysis (per ISO/DIS 11318 for the DF-1, ISO/DIS 5841-3 for the IS-1)	3-10	Met Acceptance Criteria
Long-Term Testing		
In-Vitro headerpost test 500 hours (per BIOTRONIK's Internal Validation Standards)	3	Met Acceptance Criteria

20

Interface Tests		
- Programming and Interrogation Range Determination - Programming Response as a Function of Load Resistance - Impact of the OPTIMA MP® Programming Device - Programmability with Electromagnetic Coupling of Electrodes and the Programming Coil - Programming during EMI - Verification of Protection against Injected Currents - Effect of Static Magnetic Fields - Test of the Transition from Normal Operating Mode to Interference Mode and Vice-Versa - Test of Protection from Malfunction during Unmodulated Electromagnetic Interference - Test of the Monitoring of Modulated Electromagnetic Interference (per EN 45502-2-2:1998, prEN 50061:1998/A1 and 1991, and BIOTRONIK's Internal Validation Standards)	1-10	Met Acceptance Criteria
System Tests		
- Magnet Behavior - Memory Self-Test - Parameter Error Detection - Power Saver and Watchdog - Communication Error Checking (per BIOTRONIK's Internal Test Designs)	1	Met Acceptance Criteria
Mobile Telephone Tests		
EMI Resistance Measurements in the Range 450 MHz to 3 GHz (per AAMI PC69)	1	Met Acceptance Criteria

Programmer Software Testing

Testing of the programmer software used to program and interrogate the Tachos DR – Atrial Tx ICD was successfully completed. The programmer software is referenced as SWM 1000/I-KDR.0.C. This software cartridge contains the operating system, applications for the Tachos DR – Atrial Tx, the Phylax AV, and the TMS 1000^{PLUS} Tachyarrhythmia Monitoring System. The software testing included a complete analysis of the available features and parameters and their programmability. The programmer software testing is summarized in Table 6. All of the tests were performed against BIOTRONIK's Internal Engineering Specification, ES 9757322 (Programmer Software Requirements).

Table 6: Summary of Programmer Software Testing

Test Condition/Specification	Quantity	Results
Programmer Software System Function Tests (SYS) (per Internal Engineering Specification, ES 9757322)		
Code Level Testing	Current Programmer Software	Met Acceptance Criteria
- Release Comparison Validation Releases		
- Verification of Implant List Configuration		
- Self-Test Data Integrity		
ECG Testing		
- ECG: Test of Display Functions		
- ECG: Test of Printer Functions		
- ECG: Test Monitoring Function with Print-out		
- Print Functions: Single Printout		
System Function Tests		
- System functions: Function Test		
- PC-Functions: Function Test		
- Response to Interface Errors		
- Service Time/Stress Test: PMS1000C Platform		
Programmer Software TMS 1000 Application Tests (IOTS) (per Internal Engineering Specification, ES 9757322)		
Performance Tests	Current Programmer Software	Met Acceptance Criteria
- IntegrationTest		
- Long-Term/Stress Test		
- Test Description Self-Test Duration IOTS		
- Start-Up Self-Test of the Defibrillator Part (Test of the Shock Charge Switch, Error Simulation)		
- Pulse Response of the Stimulation Outputs as a Function of the Pulse Parameters and the Charge		
- Electrical Neutrality (Pacemaker Part)		
- Incoming Sensitivity		
- Verification of the High-Rate Protection		
- Measurement of Refractory Period after Pace in A and V		
Function Tests		
- User Scenario Test		
- Verification of the Burst Stimulation (Fibrillation)		
- Test of the Test Function "Impedance Test"		
Screen Interface Tests		
- PC Function: Screen verification (Screen)		
- Test of all Texts (Screen & Printouts)		
Programmer Software for Tachos DR Application Tests (MKEA) (per Internal Engineering Specification, ES 9757322)		
Function Tests		

Test Condition/Specification	Quantity	Results
- P-R Measurement - Programmer Threshold Test - Display of Tachycardia Diagnostics Data - Display of Rate-Adaptive Holter Data - Realtime ECG - Master Therapy Switch - User Scenario Tests	Current Programmer Software	Met Acceptance Criteria
Software Performance Tests		
- Conflict Identification on Entry - Conflicts Block Transmission of Program or Operation - Display Rules - Fuel (Display, and ERI and EOS) - Auto Capacitor Reform Timing - Safety Lockouts of Manual Shock - Emergency Pacing Error Recovery - Emergency Program Key Availability - Safe Key can Interrupt other Operations - Wand Safe Key Availability - Operation of System Reset - Serial Number Communication Error - Interrogation of High-/Low-Risk Errors - Lockouts on Pacemaker Version Number - High Current Warning for Programs and Other Settings - Emergency Pacing Parameter Transposition - Programmer User Test - RAM Code Integrity - Changes in Display of Device Name - Interrogation of Parameter Set Containing an Error - Device Confidence Test		
Default Parameters Tests and Misc.		
- Standard Parameter Check - Safe Parameter Check - Review of Validation Documentation		

Bench Testing

Bench testing of BIOTRONIK's Tachos DR - Atrial Tx ICD and Programmer Software as detailed above was successfully completed.

Biocompatibility (ICD)

All tissue-contacting materials of BIOTRONIK's ICD are currently used in BIOTRONIK market-released products in the US. Biocompatibility testing of all tissue-contacting

materials used in BIOTRONIK's ICDs was successfully completed for other market released BIOTRONIK products and therefore no additional biocompatibility testing was performed.

Animal Studies

BIOTRONIK, Inc. has not performed additional animal testing with the Tachos DR - Atrial Tx in support of the PMA Supplement application beyond what was submitted with Supplement 1 for the Tachos DR ICD (P000009/S1).

X. SUMMARY OF CLINICAL STUDY

Study Overview

The purpose of this study was to demonstrate the ability of the Tachos DR - Atrial Tx to detect and convert atrial tachyarrhythmias in patients that require standard ICD therapy and that have a history or significant risk of atrial tachyarrhythmias. The ICD is not intended for use in patients with only atrial tachyarrhythmias. All patients were implanted with the Tachos DR - Atrial Tx and then had both atrial and ventricular detection and therapy features enabled. All patients received standard anti-arrhythmic drug therapy as deemed appropriate by the investigator. The patients were followed at 1, 3, and 6 months post-implant thereafter.

Induction and conversion of induced atrial and ventricular tachyarrhythmias was required after enrollment (or implant of the device). Stored data that documents the detection and conversion of spontaneous and induced atrial tachyarrhythmia episodes was retrieved from the implanted device. The atrial therapy features were enabled throughout the duration of the study.

Methods

The Tachos DR - Atrial Tx ICD was evaluated during the Tachos Atrial Conversion Therapy (TACT) Clinical Investigation. The TACT study was a multi-center, non-randomized clinical investigation conducted at 15 U.S. centers. The study had two predefined primary and five secondary endpoints.

The endpoints are listed below:

- Primary Endpoint 1: AT/AF Detection Sensitivity (Effectiveness)
- Primary Endpoint 2: Complication-Free Survival Rate (Safety) at 6 months
- Secondary Endpoint 1: Overall AT/AF Conversion Rate
- Secondary Endpoint 2: Atrial Shock Therapy Conversion Rate
- Secondary Endpoint 3: Atrial Burst Therapy Conversion Rate
- Secondary Endpoint 4: Atrial ATP Therapy Conversion Rate
- Secondary Endpoint 5: Quality of Life

This study was designed to demonstrate the effectiveness of the Tachos DR Atrial Tx to detect and convert atrial tachyarrhythmias in patients that require standard ICD therapy and that have a history or significant risk of atrial tachyarrhythmias. The safety of the device was tested through analysis of the complication-free survival rate. Additionally, the change in the quality of life (QOL) of the patient was evaluated by comparing a symptom checklist for baseline obtained at the time of enrollment and the one obtained at the three-month follow-up. A validated, symptom specific instrument for cardiac arrhythmias (Symptom Checklist – Frequency and Severity Scale[1]) was used to collect this supporting data.

Patient Selection Criteria

Inclusion criteria:

- Standard ICD indication
- History or significant risk of atrial tachyarrhythmias

Exclusion criteria:

- Have a life expectancy of less than six months
- Expected to receive heart transplantation within six months
- Enrolled in another cardiovascular clinical investigation
- Require a separate bradycardia pacemaker
- Atrial tachyarrhythmia refractory to cardioversion shock therapy

Patient Population Studied

BIOTRONIK began the TACT clinical investigation with the first US implant on December 21, 2000. As of February 1, 2002, 119 patients were being actively followed in the clinical study. Figure 1 provides a patient accountability flowchart for the 134 patients enrolled into the TACT clinical investigation.

[1] Bubien, R. Effect of Radiofrequency Catheter Ablation on Health-Related Quality of Life and Activities of Daily Living in Patients with Recurrent Arrhythmias, Circulation 1996, Vol. 94, No. 7, 1585-1591.

Figure 1 Patient Accountability Flowchart

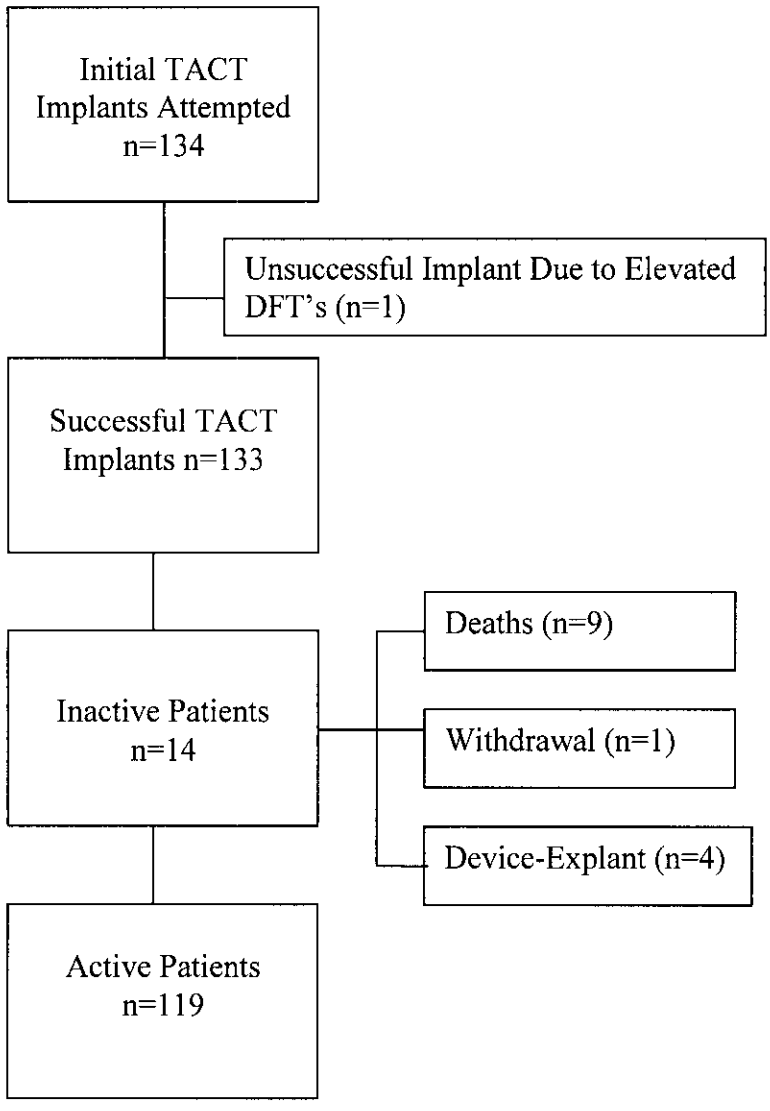


Table 7 provides a summary of the demographics of the patients enrolled in the TACT clinical study. Note that the percentage in some categories may total more than one hundred because several categories allow more than one response. In some cases, complete demographic data was not provided for all patients.

Table 7: Patient Characteristics

Characteristic	Results
Age at Implant (Years)	
Mean ± SE	68 ± 0.9
Range	46 to 86
Gender	
Male	107 (79.9%)
Female	27 (20.1%)
New York Heart Association Class	
Class I	14 (10.4%)
Class II	71 (53.0%)
Class III	45 (33.6%)
Class IV	2 (1.5%)
Unclassified	2 (1.5%)
Left Ventricular Ejection Fraction (%)	
Mean ± SE	31 ± 1.2
Range	5 to 70
Primary Cardiac Disease	
CAD/Ischemic Cardiomyopathy	99 (73.9%)
Nonischemic or Dilated Cardiomyopathy	21(15.7%)
Valvular Disease	6 (4.5%)
Primary Electrical Disease	5 (3.7%)
Other Cardiac Disease	3 (2.2%)
Primary Ventricular Tachyarrhythmias	
MVT	95 (70.9%)
VF/PVT	45 (33.6%)
Atrial Tachyarrhythmia Risk Factors	
Documented History	96 (71.6%)
Significant History	38 (28.4%)

Results

The cumulative implant duration is 896.3 months with average implant duration of 6.7 ± 0.3 months. A total of 110 patients had an implant duration of greater than 90 days during the study period of December 21, 2000 (the first implant of the Tachos DR-Atrial Tx) through February 1, 2002.

Follow-up Compliance

The follow-up compliance rate is equal to the total number of completed follow-ups divided by the total number of required follow-ups (missed and completed). There were 551 completed follow-ups out of a total of 561 required follow-ups. Therefore, the overall compliance rate is 98.2%. Table 8 outlines the follow-up compliance for all required follow-up intervals specified by the protocol.

Table 8: Follow-up Compliance Summary

Required Follow-up Interval	Follow-up Compliance # Compliant/Total Required (%)
Implant	143/143 (100.0%)
Pre-Discharge Follow-up	130/131 (99.2%)
One-Month Follow-up	111/117 (94.9%)
Three-Month Follow-up	102/102 (100.0%)
Routine Follow-up (every 6 months post-implant)	67/68 (98.5%)
All Required Follow-ups	**551/561 (98.2%)**

Primary Endpoint 1: AT/AF Detection Sensitivity (Effectiveness)

The purpose of primary endpoint 1 is to evaluate the AT/AF detection sensitivity, which is the ability of the atrial detection algorithm to appropriately detect AT (atrial tachycardia) and AF (atrial fibrillation). This endpoint was evaluated based on the review of stored electrograms following induction of AT/AF during supervised testing performed at implant and subsequent follow-ups. Of the 133 patients available for AT/AF induction testing, 14 were non-inducible or had non-sustained AT/AF, 2 were unstable and did not undergo AT/AF induction testing, and 2 were in refractory AT/AF. In addition, 1 had missing implant IEGMs data (source documentation). Therefore, data from 114 patients were available for evaluation of the primary endpoint.

Table 9 provides a summary of the results based on evaluations completed in the 114 patients. Some patients may have more than one type of atrial arrhythmia induced. Therefore the total number of patients will be less than the number of patients with each arrhythmia type.

Table 9: AT/AF Detection Sensitivity

Initial Arrhythmia	Patient	Episod	Appropria Detection
AT/AFl	40	80	77 (96.3%
AF	95	211	206 (97.6%
All Atrial Arrhythmias	114	291	283 (97.3%

Primary Endpoint 2: Complication-Free Survival Rate (Safety)

The purpose of primary endpoint 2 is to evaluate the safety of atrial therapy. This endpoint includes all complications, which are adverse events that require additional

invasive intervention to resolve. The estimate of complication-free survival at six months is based on a Kaplan-Meier actuarial analysis.

There were a total of 23 complications in 23 patients during the TACT clinical study. A summary of the complications is provided in Table 10 below. One patient had both an atrial and a ventricular lead repositioning during one procedure, which is counted as one complication. Therefore the number of patients and events in each category of the Lead-Related complications are not equal to the actual Lead-Related total number of patients and complications.

Table 10: Complication Summary

Category	Number of Patients	Percentage of Patients	Number of Complications	Complication per patient-year
Lead-Related				
Atrial Lead Repositioning	10	7.5%	10	0.13
Ventricular Lead Repositioning	4	3.0%	4	0.05
Non-Lead Related				
Medical	5	3.7%	5	0.07
Device-Related	3	2.2%	3	0.04
Elevated DFT's	2	1.5%	2	0.03
Total Lead-Related	**13**	**9.7%**	**13**	**0.17**
Total Non-Lead Related	**10**	**7.5%**	**10**	**0.13**
Overall Complication Totals	**23**	**17.2%**	**23**	**0.31**

Number of Patients = 134, Number of Patient-Years = 74.7

The Kaplan-Meier complication-free survival estimates for typical implant durations are shown in Table 11. The Kaplan-Meier complication-free survival graph is shown in Figure 2.

Table 11: Complication-Free Survival - Kaplan-Meier

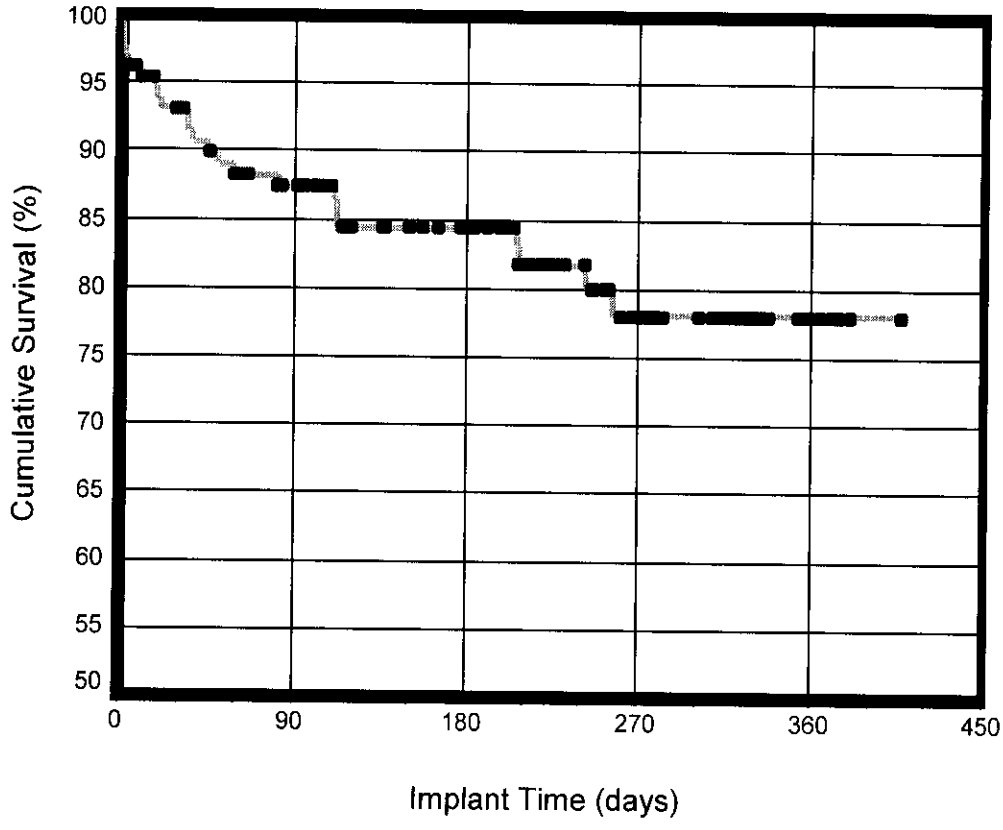
Implant Duration (Months)	Number of Patients	Cumulative Survival (S)	Standard Error (SE)*	95% Confidence Interval**
3	100	87.4%	3.1%	(81.3%, 93.5%)
6	73	84.4%	3.9%	(76.8%, 92.0%)
9	37	78.0%	6.0%	(66.2%, 89.8%)
12	7	78.0%	13.8%	(51.0%, 100.0%)

Number of Patients = 134, Number of Patient-Years = 74.7

* Peto et al adjusted

** S ± 1.96 SE

Figure 2: Complication-Free Survival – Kaplan-Meier Graph



The lower bound of the two-sided 95% confidence interval at six months (76.8%) is below the stated equivalence limit of 88% (95% - δ, where δ = 7%), as is the lower bound of the one-sided 95% confidence interval (78.0%). The null hypothesis is not rejected, and it is concluded that the complication-free rate is not equivalent to 95% within 7%. However, there were no reported complications related to atrial therapy, which supports the safety of the atrial detection and therapy features of the ICD. Furthermore, there were no study patients that experienced either a CVA (cerebrovascular accident) or stroke during this study. However, out of the 134 enrolled patients, 13 patients (9.7%) had lead-related complications and 10 (7.5%) had non-lead related types of complications. Again, none of these complications were related to the atrial detection or therapy features that are being evaluated as the focus of this clinical investigation.

Secondary Endpoints

The clinical study had five pre-defined secondary endpoints, which provided other pertinent information on the Tachos DR – Atrial Tx ICD performance. These secondary endpoints are listed below and the results from spontaneous episodes that occurred over the implant duration (up to 14 months) are combined in Table 12 and Table 13.

1. Overall AT/AF Conversion Rate

The purpose of secondary endpoint 1 is to evaluate the overall ability of the device to appropriately convert AT (atrial tachycardia) and AF (atrial fibrillation).

2. Shock Therapy Conversion Rate

The purpose of secondary endpoint 2 is to evaluate the ability of shock therapy to convert atrial tachycardia and atrial fibrillation (AT/AF).

3. Atrial HF Burst Therapy Conversion Rate

The purpose of secondary endpoint 3 is to evaluate the ability of atrial high frequency (HF) burst therapy to convert atrial tachycardia and atrial fibrillation (AT/AF).

4. Atrial ATP Therapy Conversion Rate

The purpose of secondary endpoint 4 is to evaluate the ability of atrial ATP therapy to convert atrial tachycardia (AT).

5. Quality of Life

The purpose of secondary endpoint 5 is to evaluate any change in the quality of life (QOL) of the patient from baseline at the time of enrollment and the three-month follow-up. A validated, symptom specific instrument for cardiac arrhythmias (Symptom Checklist – Frequency and Severity Scale[2]) will be used to collect this supporting data. This instrument is formatted in the form of two symptom checklists and quantifies both symptom frequency and severity. The format allows respondents to use check marks to indicate both the frequency with which they have experienced each symptom and the severity for each symptom listed. Since the Symptom Checklist quantifies two aspects of symptom assessment: two independent scores are produced.

Table 12 includes the success of the therapy sequences for spontaneous episodes and Table 13 includes the total number of spontaneous episodes and subsequent success of each atrial therapy and the quality of life data.

[2] Bubien, R. Effect of Radiofrequency Catheter Ablation on Health-Related Quality of Life and Activities of Daily Living in Patients with Recurrent Arrhythmias, Circulation 1996, Vol. 94, No. 7, 1585-1591.

Table 12: Atrial Therapy Sequences success Detail

#	Therapy Sequences	Patients	Episodes	Successes	Success Rate
1	ATP	14	57	35	61.4%
2	ATP, HF Burst	8	14	5	35.7%
3	ATP, HF Burst, Shock	4	6	5	83.3%
4	ATP, Shock	3	3	2	66.7%
5	HF Burst	24	214	105	49.1%
6	HF Burst, Shock	14	26	22	84.6%
7	Shock	15	27	18	66.7%
All Therapy Sequences		43	347	192	55.3%

Table 13: Secondary Endpoint Results

Secondary Endpoint Description	**Result** [95% CI]
1. Overall AT/AF Conversion Rate	55.3% (192 out of 347 episodes) [49.9%, 60.6%]
2. Shock Therapy Conversion Rate	74.1% (46 out of 62 episodes) [61.5%, 84.5%]
3. Atrial HF Burst Therapy Conversion Rate	42.3% (110 out of 260 episodes) [36.2%, 48.6%]
4. Atrial ATP Therapy Conversion Rate	45.0% (36 out of 80 episodes) [33.8%, 56.5%]
	Result (p-value)
5. Quality of Life • Improvement in average frequency • Improvement in average severity	 6.9 ($p < 0.001$) 5.7 ($p < 0.001$)

Additional Results

The TACT clinical study allowed the use of all commercially available atrial leads. However, a BIOTRONIK dual-coil ICD lead was required. Table 14 and Table 15 provide a summary of the various lead types used during the course of the study. Note that the tables include only leads that are from the initial implanted system.

Table 14: Atrial Leads

Manufacturer & Lead Model	Number and Percentage of All Implanted Leads
Biotronik	
Elox	73 (54.8%)
Retrox	20 (14.9%)
Synox	11 (8.2%)
Polyrox	8 (6.0%)
Guidant	
Fineline	2 (1.5%)
Fineline EZ	1 (0.7%)
Medtronic	
CapSureFix	7 (5.2%)
CapSureFix Novus	2 (1.5%)
CapSureZ Novus	2 (1.5%)
Oscor Medical	
Oscor	1 (0.7%)
St. Jude	
Tendril SDX	5 (3.7%)
Tendril	1 (0.7%)
Tendril DX	1 (0.7%)
All Models	**134 (100%)**

Table 15: ICD Leads

Manufacturer & Lead Model	Number and Percentage of All Implanted Leads
Biotronik	
Kainox SL	132 (98.5%)
SL-ICD	1 (0.75%)
Medtronic	
Sprint	1 (0.75%)
All Models	**134 (100%)**

The one patient implanted with a Medtronic ICD lead (Table 15) required an active-fixation dual-coil ICD lead due to patient's anatomy and multiple unsuccessful attempts at re-positioning the ventricular lead during the implant procedure.

Table 16 represents the lead measurement data obtained during the implant procedure, 3 month follow-up interval, and other follow-ups which generally occurred beyond the 3 month follow-up interval.

Table 16: Lead Measurements

Lead Measurement	Implant	3-Month Follow-up	Other Follow-ups
P-Wave (millivolts)			
Number of Tests	142	97	239
Mean ± SE	3.2 ± 0.1	3.4 ± 0.2	3.0 ± 0.1
Range	0.8 to 6.3	0.4 to 6.3	0.4 to 6.3
Atrial Pacing Threshold @ 0.5 ms (Volts)			
Number of Tests	134	92	205
Mean ± SE	0.8 ± 0.1	1.2 ± 0.1	1.2 ± 0.1
Range	0.2 to 5.8	0.2 to 5.8	0.1 to 6.6
Atrial Pacing Impedance (Ohms)			
Number of Tests	141	101	244
Mean ± SE	453 ± 10.0	473 ± 17.0	477 ± 11.7
Range	330 to 950	320 to 1210	280 to 1250
R-Wave (millivolts)			
Number of Tests	142	99	249
Mean ± SE	12.2 ± 0.1	12.9 ± 0.4	12.0 ± 0.2
Range	2.8 to 16.0	3.0 to 16.0	2.1 to 16.0
Ventricular Pacing Threshold @ 0.5 ms (Volts)			
Number of Tests	138	101	224
Mean ± SE	0.6 ± 0.0	1.2 ± 0.1	1.2 ± 0.1
Range	0.2 to 1.7	0.4 to 6.8	0.3 to 7.2
Ventricular Pacing Impedance (Ohms)			
Number of Tests	142	101	244
Mean ± SE	589 ± 10.0	582 ± 10.8	551 ± 7.0
Range	410 to 920	280 to 870	270 to 970

Ventricular Tachyarrhythmias

The ICD is designed to provide ventricular tachyarrhythmia therapy in addition to atrial tachyarrhythmia therapy. All patients are required to have standard ventricular ICD indications prior to enrollment. Information about the episodes of VT/VF was also collected during the study as additional data of interest. Table 17 provides a summary of the spontaneous ventricular tachyarrhythmias detected and resulting in appropriate ventricular therapy during the study. Note that some patients may have had more than one arrhythmia type. Therefore, the total number of patients will be less than the number of patients with each arrhythmia type.

Table 17: Spontaneous VGT/VF Episodes

Detection Zone	Number of Patients	Number of Episodes	Successful Conversion	% Success
VT-1/VT-2	11	152	152	100%
VF	10	30	30	100%
Totals	17	182	182	100%

Atrial Tachyarrhythmia Conversion Testing

Atrial conversion testing was performed to assess the atrial DFT shock energy. The protocol required two atrial conversions of AT/AF. This was accomplished by atrial inductions followed by delivery of either device initiated cardioversion shocks or manual shocks delivered through the device. The investigators were instructed to wait a minimum of one minute after AT/AF induction prior to assessing the atrial DFT. If the first cardioversion shock was unsuccessful, a higher energy shock was delivered until cardioversion was achieved or until the maximum cardioversion energy was reached. Investigators employed varied testing methods including: true step-up testing, step-down testing, inducing and converting dual arrhythmias simultaneously or simply completing two atrial conversions at an energy that would provide an adequate conversion safety margin. Therefore the data presented in the following table may not accurately reflect the true atrial DFT.

Table 18 provides a summary of the atrial DFT results during implantation and separate results for follow-up testing. Atrial DFT testing was only required by the protocol during the implant procedure. However, the investigators were encouraged to induce atrial tachyarrhythmias at subsequent follow-ups. Some patients may have more than one type of atrial arrhythmia induced. Therefore the total number of patients will be less than the number of patients with each arrhythmia type. 115 of 134 patients had inducible atrial tachyarrhythmias at implant.

Table 18: Atrial Defibrillation Thresholds

Type of Tests	Results at Implant (Joules)	Results at Follow-Ups (Joules)
Lowest Converting Energy (AF)		
Number of Patients	91	17
Mean ± SE	6.1 ± 0.6	11.8 ± 0.8
Range	1 to 30	3 to 30
Lowest Converting Energy (AT/AFl)		
Number of Patients	30	4
Mean ± SE	5.2 ± 0.9	4.8 ± 0.5
Range	1 to 20	2 to 10

Inappropriate Atrial Episodes

During the TACT study, 1021 atrial episodes have been detected in the AT/AF zones. However, in some cases episodes were inappropriately detected as atrial tachyarrhythmia episodes. Inappropriate atrial episodes are defined as atrial episodes detected by the device when the patient was not in an atrial arrhythmia. Far-filed oversensing of the ventricular channel due to sub-optimal programming of atrial detection parameters or an atrial lead dislodgement were the primary causes of inappropriate atrial detection. As a result, inappropriate atrial detection was usually resolved by either reprogramming the ICD by extending the Ablank_Vsense and /or Ablank_Vpage parameters, decreasing the atrial sensitivity or by performing an atrial lead revision.

Table 19 summarizes the incidence of spontaneous inappropriate atrial episodes. Both the numbers of patients and episodes are not mutually exclusive since some patients had more than one type of therapy delivered and some episodes had more than one type of therapy delivered.

Table 19: Inappropriately Detected Atrial Episodes

Inappropriate Episode Category	Number (%) of Total Patients n = 134	Number (%) of All Episodes n = 1021
No Atrial Therapy Delivered	13 (9.7%)	38 (3.7%)
Inappropriate Atrial Therapy Delivered:	11 (8.2%)	133 (13.0%)
Atrial ATP	7* (5.2%)	66* (6.5%)
HF Burst	5* (3.7%)	67* (6.6%)
Atrial Shock	2* (1.5%)	3* (0.3%)
Total/causes of Inappropriate Detection:	19 (14.2%)	171 (16.7%)
Far-field Oversensing of the Ventricular Channel	19* (14.2%)	170 (16.7%)
Paced Ventricular Atrial Refractory Period Programming	1* (0.7%)	1 (0.1%)

* Not mutually exclusive. Patients or episodes may have included more than one type of inappropriate atrial detection or inappropriate therapy.

Multi-site Poolability and Gender Analysis

The clinical report includes data from multiple centers with centralized coordination, data processing, and reporting at BIOTRONIK. All of the clinical centers followed the requirements of an identical clinical protocol, and all of the clinical centers used the same methods to collect and report the clinical data. In order to justify pooling of the data from multiple centers, several analyses were completed. All of the centers were divided into two groups based on implant volume. Comparisons were then made between the patient populations based on the results of each of the endpoints. Additionally, analyses were performed on the data collected in the IDE clinical investigation in order to compare results between males and females. The first type of analysis compared enrollment by patient gender to other clinical studies. The second type of analysis compared the safety and efficacy in each gender.

The results of these analyses demonstrate poolability of the data between sites. There were no significant differences in the second primary endpoint or any of the secondary endpoints between high and low volume implant centers. There was a significant difference in the adjusted atrial detection rate between patients enrolled at low volume sites and those at high volume sites. However, the atrial detection rates in both groups exceeded the 87% target rate.

The gender distribution in this clinical investigation is consistent with other clinical studies and includes a representative proportion of female participants. There were no significant differences in any of the primary or secondary endpoints between the male and female population.

XI. CONCLUSIONS DRAWN FROM STUDIES

The pre-clinical testing demonstrated that the Tachos DR – Atrial Tx ICD operates according to system performance specifications.

The clinical data support the following conclusions regarding the safety and effectiveness of the Tachos DR – Atrial Tx ICD:

- The atrial tachyarrhythmia detection rate exceeded both the equivalence limit of 80% (87% - the clinically significant difference of 7%) and the lower bounds of the 95% confidence interval proposed in the protocol, the null hypothesis is rejected. The requirement of equivalence to a rate of 87% within a clinically significant difference of 7% is satisfied. These results demonstrate that the Tachos DR - Atrial Tx provides appropriate detection of atrial tachyarrhythmias.

- The total number of complications observed during the study was higher than expected. However, none of these events were related to the investigational atrial detection or therapy features. Additionally no cerebrovascular accidents (CVA's)

have been reported during the clinical study. As a result, the clinical data gathered during this study clearly demonstrate the safety of these new features.

In accordance with the above conclusions, the clinical data provides reasonable assurance that the Tachos DR – Atrial Tx ICD is safe and effective for the treatment of conditions requiring an ICD with atrial tachyarrhythmia therapies as specified in the indications for use.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

The clinical data provided a reasonable level of safety and effectiveness of the Tachos DR - Atrial Tx ICD. Even though the sponsor did not meet the pre-defined safety endpoint, the events were not considered to be related to the uniqueness of the device and the overall complication rate was still within acceptable clinical limits. There were some instances of inappropriate detection that were able to be fixed with programming changes or repositioning the atrial lead. Based on the reviews of the PMA application for the Tachos DR - Atrial Tx ICD, FDA determined that the device provides reasonable assurance of safety and effectiveness when used as labeled.

FDA issued an approval order on September 9, 2002.

The applicant's manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.